

(19) World Intellectual Property
Organization
International Bureau



540511
24 JUN 2005



(43) International Publication Date
22 July 2004 (22.07.2004)

PCT

(10) International Publication Number
WO 2004/060374 A1

(51) International Patent Classification⁷: **A61K 31/496**,
31/381, 31/343, 31/15, 31/4525, 31/135, A61P 25/24

(21) International Application Number:
PCT/JP2003/016724

(22) International Filing Date:
25 December 2003 (25.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
NO. 2002-379003
27 December 2002 (27.12.2002) JP
60/470,481 14 May 2003 (14.05.2003) US

(71) Applicant (for all designated States except US): **OTSUKA PHARMACEUTICAL CO., LTD.** [JP/JP];
9, Kanda-Tsukasacho 2-chome, Chiyoda-ku, Tokyo
101-8535 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KIKUCHI, Tetsuro**
[JP/JP]; 157-13, Kawauchicho Komatsunishi, Tokushima-

shi, Tokushima 771-0104 (JP). **IWAMOTO, Taro** [JP/US];
36, Boundinot Street, Princeton, NJ 08540 (US). **HIROSE,**
Tsuyoshi [JP/JP]; 8-9-502, Sakoichibancho, Tokushima-
shi, Tokushima 770-0021 (JP).

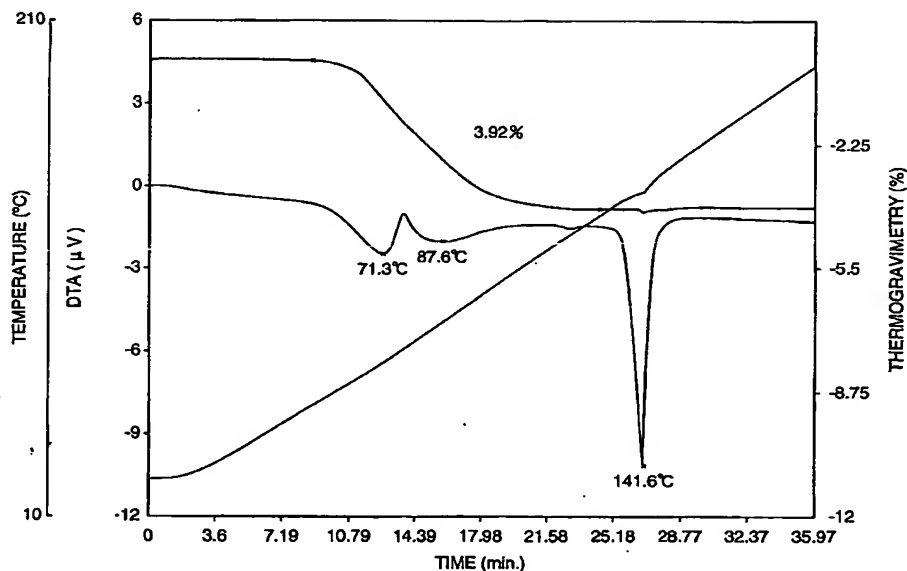
(74) Agents: **ASAMURA, Kiyoshi** et al.; Room 331, New
Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku,
Tokyo 100-0004 (JP).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: **CARBOSTYRIL DERIVATIVES AND SEROTONIN REUPTAKE INHIBITORS FOR TREATMENT OF MOOD DISORDERS**



(57) Abstract: The pharmaceutical composition of the present invention comprises (1) a carbostyryl derivative and (2) a serotonin reuptake inhibitor in a pharmaceutically acceptable carrier. The carbostyryl derivative may be aripiprazole or a metabolite thereof, which is a dopamine-serotonin system stabilizer. The serotonin reuptake inhibitor may be fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline or escitalopram. The pharmaceutical composition of the present invention is useful for treating patients with mood disorders, particularly depression or major depressive disorder.

WO 2004/060374 A1



Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PO P 03/16724

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/496 A61K31/381 A61K31/343 A61K31/15 A61K31/4525
A61K31/135 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/156067 A1 (SVENSSON TORGN Y ET AL) 24 October 2002 (2002-10-24) claims 1-10	1-3, 6, 8-15, 18, 20-27, 30, 32-36
Y	WO 02/060423 A (OTSUKA PHARMA CO LTD) 8 August 2002 (2002-08-08) cited in the application claims 1-5 -/-	1-36

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

G document member of the same patent family

Date of the actual completion of the International search

6 May 2004

Date of mailing of the International search report

08/06/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Leherte, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 03/16724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAWLER ET AL: "Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes" NEUROPSYCHOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHING, NEW YORK, NY, US, vol. 20, no. 6, June 1999 (1999-06), pages 612-627, XP002205416 ISSN: 0893-133X abstract	1-3, 6-15, 18-27, 30-36
Y	BURRIS K D ET AL: "ARIPIPRAZOLE, A NOVEL ANTIPSYCHOTIC, IS A HIGH-AFFINITY PARTIAL AGONIST AT HUMAN DOPAMINE D2 RECEPTORS" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 302, no. 1, July 2002 (2002-07), pages 381-389, XP001087706 ISSN: 0022-3565 abstract	1-3, 6-15, 18-27, 30-36
Y	GOODMAN ET AL: "THE PHARMACOLOGICAL BASIS OF THERAPEUTICS" , PHARMACOLOGICAL BASIS OF THERAPEUTICS, GOODMAN GILMAN'S PHARMACOLOGICAL BASIS OF THERAPEUTICS, NEW YORK, PERGAMON PRESS, US, VOL. ED. 10, PAGE(S) 451, 468 , 2001 XP002279121 page 451, column 2, paragraph 2 page 468, column 1, paragraph 4	1-36
P,X	PRESKORN S H: "Relating clinical trials to psychiatric practice: Part I: The case of a 13-year old on aripiprazole and fluoxetine" JOURNAL OF PSYCHIATRIC PRACTICE 2003 UNITED STATES, vol. 9, no. 4, July 2003 (2003-07), pages 307-313, XP008029355 ISSN: 1527-4160 page 307, column 2, paragraph 2 page 308, column 2, paragraph 3	1-3,6, 8-15,18, 20-27, 30,32-36
P,X	GREEN B: "FOCUS ON ARIPIPRAZOLE" CURRENT MEDICAL RESEARCH AND OPINION, HANTS, GB, vol. 20, no. 2, 12 December 2003 (2003-12-12), pages 207-213, XP008029340 page 211, column 2, paragraph 12	1-3,6, 8-15,18, 20-27, 30,32-36
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 03/16724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 2004/010932 A (MIGALY PETER) 5 February 2004 (2004-02-05)</p> <p>claims 19,23,31</p>	<p>1-3,6, 8-15,18, 20-27, 30,32-36</p>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-36

The terms "carbostyryl derivative" and "metabolite of aripiprazole" used in claims 1, 2, 4, 6-14, 16, 18-26, 28, 30-36 are vague and unclear and leave the reader in doubt as to the meaning of the technical features (i.e. the compounds) to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). Independent of the above, the Applicant has not provided any test to demonstrate whether a compound is a metabolite of aripiprazole or not. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which compounds fall within the definition.

Claims 1-36 encompass a genus of compounds defined only by their function ("dopamine-serotonin system stabilizer" and "serotonin reuptake inhibitor"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

Present claims 9, 11, 13-21, 23, 25-33 and 35 relate to an extremely large number of disease states. The therapeutic application is defined as "mood disorders" or even "disorders" which does not allow any practical application in the form of a defined, real treatment of a pathological condition. It is noted that any disease may represent a disorder. A lack of clarity (and/or conciseness) within the meaning of Art. 6 PCT therefore arises.

Independent of the above, the Applicant has not provided any test to demonstrate whether a disease is a mood disorder or not. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which diseases fall within the definition.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compositions comprising aripiprazole, dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or N-(2,3-Dichlorophenyl)piperazine in combination with fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline or escitalopram in relation to their use in the treatment of depression or major depressive disorder.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 03/16724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-36
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 03/16724

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 2002156067	A1	24-10-2002	CA	2431041 A1	11-07-2002
			EP	1353675 A2	22-10-2003
			WO	02053140 A2	11-07-2002
WO 02060423	A	08-08-2002	BR	0206237 A	23-12-2003
			CA	2429496 A1	08-08-2002
			CN	1484524 T	24-03-2004
			EP	1355639 A2	29-10-2003
			WO	02060423 A2	08-08-2002
WO 2004010932	A	05-02-2004	WO	2004010932 A2	05-02-2004